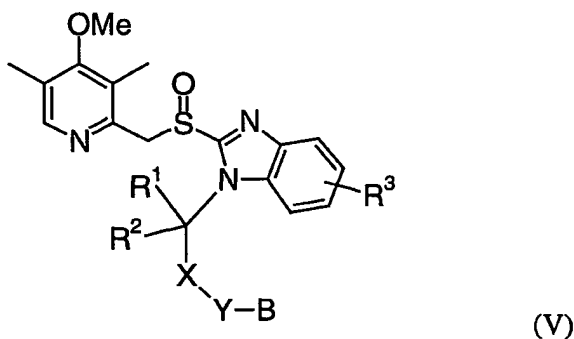


5. A process for the preparation of a compound of formula I according to any one of claims 1 to 3 comprising the step of reacting a compound of Formula V



wherein

R^1 is hydrogen or C_1 - C_6 alkyl,

R^2 is hydrogen or C_1 - C_6 alkyl,

R^3 is methoxy linked to the carbon atom in position 5 or linked to the carbon atom in position 6 of the benzimidazole moiety,

B is $-Br$ or $-Cl$,

X is $-O-C(=O)-O-$, $-O-C(=O)-N-$, or $-O-C(=O)-CH_2-$,

Y is $-(CH_2)_n-$, $-(CH_2)_m-O-(CH_2)_p-$, or a single bond, and

m, n, and p are integers and independently selected from 1 to 10.

with silver nitrate in a suitable solvent, such as acetonitrile under standard conditions to give compounds of Formula I wherein

R^1 is hydrogen or C_1 - C_6 alkyl,

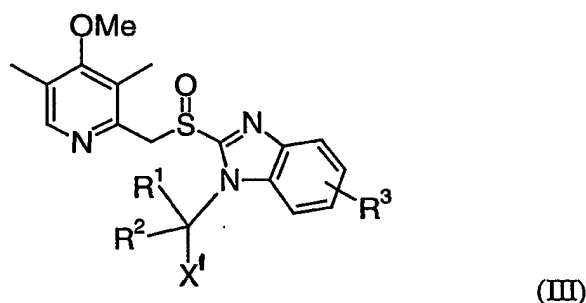
R^2 is hydrogen or C_1 - C_6 alkyl,

X is $-O-C(=O)-O-$, $-O-C(=O)-N-$, or $-O-C(=O)-CH_2-$,

Y is $-(CH_2)_n-$, $-(CH_2)_m-O-(CH_2)_p-$, or a single bond, and

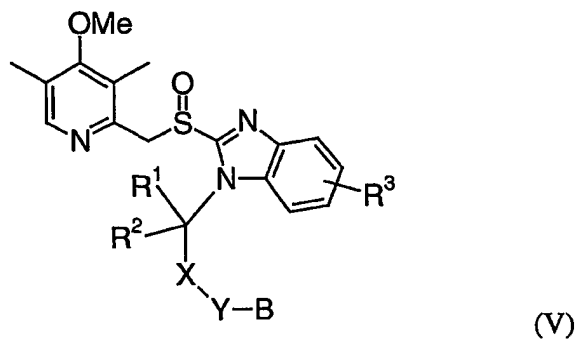
m, n, and p are integers and independently selected from 1 to 10.

6. A compound of formula I according to any one of claims 1 to 3 for use in therapy.
7. A pharmaceutical formulation containing at least one compound of formula I according to any one of claims 1 to 3 as active ingredient in combination with a pharmaceutically acceptable diluent or carrier.
8. Use of a compound of formula I according to any one of claims 1 to 3 for the manufacture of a medicament for the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori*.
9. A method for the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori*, which comprises administering to a mammal, including humans, in need of such treatment an effective amount of a compound of formula I according to any one of claims 1 to 3.
10. A compound of the formula III



wherein R¹ is hydrogen or C₁-C₆ alkyl,
 R² is hydrogen or C₁-C₆ alkyl,
 R³ is methoxy linked to the carbon atom in position 5 or linked to the carbon atom in position 6 of the benzimidazole moiety, and
 X¹ is halogen, such as chloride.

11. A compound of the formula V



wherein

R^1 is hydrogen or C_1 - C_6 alkyl,

R^2 is hydrogen or C_1 - C_6 alkyl,

R^3 is methoxy linked to the carbon atom in position 5 or linked to the carbon atom in position 6 of the benzimidazole moiety,

B is $-Br$ or $-Cl$,

X is $-O-C(=O)-O-$, $-O-C(=O)-N-$, or $-O-C(=O)-CH_2-$,

Y is $-(CH_2)_n-$, $-(CH_2)_m-O-(CH_2)_p-$, or a single bond, and

m, n, and p are integers and independently selected from 1 to 10.

12. A pharmaceutical combination containing at least one compound of formula I according to any one of claims 1-3 and at least one other antibacterial compound in one single or separate dosage form for simultaneous, separate or sequential use in the prevention or treatment of bacterial infections, optionally together with one or more pharmaceutically acceptable diluents or carriers.

13. A pharmaceutical combination according to claim 12, wherein the at least other antibacterial compound is selected from any one of β -lactam antibiotics, macrolides, tetracyclines, aminoglycosides and quinolones.
- 5 14. A pharmaceutical combination containing at least one compound of formula I according to any one of claims 1-3 and at least one NSAID in one single or separate dosage form for simultaneous, separate or sequential use in the prevention or treatment of bacterial infections.
- 10 15. A pharmaceutical combination according to claim 14, wherein the NSAID is selected from any one of ibuprofen, indomethacin, diclofenac, ketorolac, naproxen, ketoprofen, mefenamic acid, flunixin, flufenamic acid and niflumic acid.
- 15 16. A pharmaceutical combination according to any one of claims 12-15, in form of a pharmaceutical formulation.
17. Use of a compound according to any one of claims 1 to 3 for the manufacture of a medicament for the treatment or prophylaxis of bacterial infections, wherein said medicament is adapted to be administered in combination with at least one other
- 20 antibacterial agent.
18. Use of a compound according to any one of claims 1 to 3 for the manufacture of a medicament for the treatment or prophylaxis of bacterial infections, wherein said medicament is adapted to be administered in combination with at least one NSAID.
- 25 19. Use of a NO-releasing PPI for the manufacture of a medicament for the treatment or prophylaxis of bacterial infections.

20. A pharmaceutical composition containing at least one NO-releasing PPI and at least one other antibacterial compound in one single or separate dosage forms for simultaneous, separate or sequential use in the prevention or treatment of bacterial infections.
- 5 21. A pharmaceutical composition containing at least one NO-releasing PPI and at least one NSAID in one single or separate dosage forms for simultaneous, separate or sequential use in the prevention or treatment of bacterial infections.
- 10 22. A kit comprising an NO-releasing PPI in combination with at least one antibacterial compound.
23. A kit comprising an NO-releasing PPI in combination with at least one NSAID.

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(54) Title: PROTECTED FORMS OF A COMBINATION OF PHARMACOLOGICALLY ACTIVE AGENTS AND USES THEREFOR

(57) Abstract: In accordance with the present invention, there are provided conjugates of a combination of pharmacologically active agents (e.g., NSAIDs and selective COX-2 inhibitors). Invention conjugates provide a new class of pharmacologically active agents (e.g., anti-inflammatory agents) which provide the therapeutic benefits of both NSAIDs and selective COX-2 inhibitors, while causing a much lower incidence of side-effects than are typically observed with such agents due to the protective effects imparted by modifying the pharmacologically active agents as described herein.

Protected Forms of a Combination of Pharmacologically
Active Agents and Uses Therefor

FIELD OF THE INVENTION

5 The present invention relates to novel conjugated forms of pharmacologically active agents, and methods for the preparation and use thereof. In a particular aspect of the invention, methods are provided for treating pathological conditions with a protected form of a combination of pharmacologically active agents, thereby reducing the occurrence of side-effects caused thereby.

10 BACKGROUND OF THE INVENTION

 Despite the advent of modern pharmaceutical technology, many drugs still possess untoward toxicities which often limit the therapeutic potential thereof. For example, although non-steroid anti-inflammatory drugs (NSAIDs) are a class of
15 compounds which are widely used for the treatment of inflammation, pain and fever, NSAIDs (e.g., naproxen, aspirin, ibuprofen and ketoprofen) can cause gastrointestinal ulcers, a side-effect that remains the major limitation to the use of NSAIDs (see, for example, J. L. Wallace, in Gastroenterol. 112:1000-1016 (1997); A. H. Soll et al., in Ann Intern Med. 114:307-319 (1991); and J. Bjarnason et al., in Gastroenterol.
20 104:1832-1847 (1993)).

 There are two major ulcerogenic effects of NSAIDs: (1) irritant effects on the epithelium of the gastrointestinal tract and (2) suppression of gastrointestinal prostaglandin synthesis. In recent years, numerous strategies have been attempted to
25 design and develop new NSAIDs that reduce the damage to the gastrointestinal tract. These efforts, however, have largely been unsuccessful. For example, enteric coating or slow-release formulations designed to reduce the topical irritant properties of NSAIDs have been shown to be ineffective in terms of reducing the incidence of clinically

significant side effects, including perforation and bleeding (see, for example, D. Y. Graham et al., in *Clin. Pharmacol. Ther.* 38:65-70 (1985); and J. L. Carson, et al., in *Arch. Intern. Med.*, 147:1054-1059 (1987)).

5 It is well recognized that aspirin and other NSAIDs exert their pharmacological effects through the non-selective inhibition of cyclooxygenase (COX) enzymes, thereby blocking prostaglandin synthesis (see, for example, J. R. Van in *Nature*, 231:232-235 (1971)). There are two types of COX enzymes, namely COX-1 and COX-2. COX-1 is expressed constitutively in many tissues, including the stomach, kidney, and platelets,
10 whereas COX-2 is expressed only at the site of inflammation (see, for example, S. Kargan et al. in *Gastroenterol.*, 111:445-454 (1996)). The prostagladins derived from COX-1 are responsible for many of the physiological effects, including maintenance of gastric mucosal integrity.

15 Many attempts have been made to develop NSAIDs that only inhibit COX-2, without impacting the activity of COX-1 (see, for example, J.A. Mitchell et al., in *Proc. Natl. Acad. Sci. USA* 90:11693-11697 (1993); and E.A. Meade et al., in *J. Biol. Chem.*, 268:6610-6614 (1993)). There are several NSAIDs presently on the market (e.g., rofecoxib and celecoxib) that show marked selectivity for COX-2 (see, for example, E.
20 A. Meade, supra; K. Glaser et al., in *Eur. J. Pharmacol.* 281:107-111 (1995) and Kaplan-Machlis, B., and Klostermeyer, BS in *Ann Pharmacother.* 33:979-88, (1999)). These drugs appear to have reduced gastrointestinal toxicity relative to other NSAIDs on the market.

25 On the basis of encouraging clinical as well as experimental data, the development of highly selective COX-2 inhibitors appears to be a sound strategy to develop a new generation of anti-inflammatory drugs. However, the physiological functions of COX-1 and COX-2 are not always well defined. Thus, there is a possibility that prostagladins produced as a result of COX-1 expression may also contribute to
30 inflammation, pain and fever. On the other hand, prostagladins produced by COX-2 have been shown to play important physiological functions, including the initiation and